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FDA's AIDS Program

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Abstract

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KEYWORDS: AIDS, program, FDA

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The Challenge of AIDS

The Conquest of AIDS — under the leadership of President Reagan — is the Nation's number one public health priority. Because of this, the Federal Government, and in particular the Public Health Service (PHS), is committed to fighting an unceasing battle against this deadly disease. For the PHS, of which FDA is a part, this has meant mounting a coordinated strategy involving research, and the development of ways to prevent, cure and treat AIDS.

FDA's special role in this battle is largely based on its general responsibilities of overseeing the safety and effectiveness of the nation's drugs and the implementation of devices to ensure the safety of the nation's blood supply. Annual sales of FDA-regulated products account for approximately 550 billion consumer dollars annually. Much progress has been made; and FDA's accomplishments to date will be detailed later in this article. However, until a safe and effective drug that cures AIDS is found, as well as a safe and effective vaccine that prevents the disease, our job will not be done and we will not rest.

Understandably, the public demands that FDA expedite its review and the approval of new products that will offer even a small measure of hope to AIDS patients and their families. FDA is taking steps to ensure the timely review and approval of AIDS-related products, as well as new drugs for other life-threatening and serious diseases. Careful FDA review is necessary and mandated by law to minimize the risk of allowing potentially unsafe and ineffective products from coming onto the market. Unsafe products cause unnecessary suffering. Ineffective ones raise false hopes, cause the patient to defer the use of other more effective measures, and are burdensome and economically costly

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The Dimensions of the Problem

The incidence of AIDS has reached epidemic proportions, both in the United States and abroad. Since its existence was first reported in 1981 up to the end of 1987, approximately 50,000 persons in the United States have contracted AIDS, and more than half of these persons have died. Up to 1.5 million additional individuals in the United States (and up to 20 million worldwide) it is estimated, are infected with the AIDS antibody, and it is feared that this number will grow to 10 million (100 million worldwide) in just four years. Absent finding a cure or at least an effective treatment for AIDS, it is feared that at worst, all — or at best, most — of these people will die before the turn of the century.

The AIDS crisis consists of three separate epidemics. The first was the silent epidemic that occurred in the late 70's, before health officials knew about the disease but after the AIDS virus has begun to spread through specific populations. In the early 80's, the second epidemic emerged when the terrible scope, nature, and symptoms of the disease began to become clear. During this stage of clinical involvement, solutions were sought but society was not yet truly alarmed. The world is just now entering the third epidemic, or the stage of societal awareness, in which there is widespread recognition of AIDS as a universal and deadly threat to which no country and no population is immune.

The Public Health Service AIDS Program

As authorized by President Reagan and Secretary Bowen, Assistant Secretary for Health Dr. Robert E. Windom has overall responsibility for coordinating the AIDS-oriented activities of agencies within the Public Health Service (PHS): The National Institutes of Health (research); the Centers for Disease Control (epidemiology); the Alcohol, Drug Abuse, and Mental Health Administration (risk reduction among drug abusers and other high-risk groups); the Health Resources and Services Administration (health services delivery); and the Food and Drug Administration (research and the evaluation of drugs, vaccines, diagnostic test kits, and protective medical devices such as surgical gloves and condoms). See Appendix A.

The overall coordination of the PHS regarding AIDS is highly structured. In 1987, HRS Secretary Bowen appointed a PHS AIDS

Executive Task Force under the leadership of Assistant Secretary for Health Windom. This task force coordinates efforts of the various PHS agencies in the areas of research, prevention, therapeutic intervention, and blood safety. Dr. Windom in turn established an Intragovernmental AIDS Health Care Delivery Task Force under the leadership of HRSA (Health Resources Services Administration) Director Dr. David Sundwall. This task force had responsibility for developing recommendations on improving health care delivery systems for AIDS patients.

In addition, PHS is placing strong emphasis on educating the general public, as well as certain high-risk groups, because without a cure or vaccine in the near future, public awareness of methods for preventing AIDS is the best hope for controlling the spread of the disease. Since 1983, PHS has operated a toll-free AIDS information hotline and distributed several hundred thousand copies of the leaflet, "Facts About AIDS," to the public. In addition, since October of 1987, PHS has distributed to the public almost a million copies of Surgeon General Koop's Report on AIDS.

FDA's AIDS Program

FDA, through its responsibilities for approving safe and effective drugs, biologics, and devices, plays a major role in the Federal Government's war on AIDS. Commissioner Young and I have designated AIDS initiatives as the Agency's number one priority, thus placing special emphasis on producing the most timely, efficient, and effective research and premarketing review possible for promising drugs, vaccines, other biologics, and medical devices for treating, curing, or preventing AIDS or AIDS-related diseases (such as opportunistic infections).

To meet the urgent demands of the AIDS crisis, FDA also will divert resources from other programs when required. Because AIDS efforts have increased over the last few years, we have responded by reorganizing the Center for Drugs and Biologics into two new productivity centers — the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research. FDA will continue to give highest priority both to new drug review in general and associated AIDS activities in particular.

FDA's Drug Review Process

Before human testing can begin for an experimental drug or vaccine, the product's sponsor or investigator must file an investigational

new drug application, or IND, with FDA. To get an IND approved, the sponsor must demonstrate, based on animal studies, that the product is reasonably safe for testing human subjects in what are known as "clinical tests" or "clinical trials".

In order to minimize risks to participants, clinical testing under an IND is normally divided into three sequential phases. Phase 1 involves the initial introduction of an investigational therapy into humans. Phase 1 studies are designed to determine pharmacologic actions of the therapy, drug metabolism, and the side effects associated with varying doses. Phase 1 usually includes less than 100 patients.

During Phase 2, the first controlled clinical studies are conducted to evaluate the effectiveness of the therapy for a particular indication and to assess relative safety. Phase 2 studies are typically well controlled (that is, a group of subjects who do not receive the therapy, the "control group" is compared to a group that does receive the therapy and other variables are controlled to assess effects of the drug) and involve no more than several hundred participants.

Phase 3 studies include expanded controlled and uncontrolled trials. They are intended to gather additional information about effectiveness, to establish proper dosing regimens, and to provide sufficient safety information to give a clear profile of the drug's potential risks. Phase 3 studies usually include from several hundred to several thousand subjects.

Once Phase 3 testing is completed, the sponsor submits the test results to FDA. In the case of a drug, the submission is in the form of a new drug application (NDA). In the case of a vaccine, the submission is in the form of a biologic license application. FDA exhaustively reviews the data submitted and decides whether the therapy can be approved for marketing. Although requirements for new drug product applications and for new biologic product license applications differ, the basic processes are similar, and products in both categories must be determined through data from adequate and well-controlled trials to be safe and effective.

FDA has always worked hard to make promising new drugs available as early in the drug development process as possible. Treatment protocols (wide availability to patients of experimental drugs for treatment — not just testing — under close physician and sponsor supervision) have been encouraged by FDA when early clinical evidence indicates a drug has real promise. Concern over access to promising AIDS drugs has focused attention on the timely access issue as never before and prompted Commissioner Young and me to revise FDA's proce-

dures for releasing experimental drugs. These new procedures, which became effective June 22, 1987, apply to serious or immediately life-threatening diseases for which no alternative therapies exist.

Approval of Zidovudine

FDA's timely approval of the anti-AIDS drug zidovudine, formerly known as azidothymidine, provides an example of how FDA's drug review system works at its best. On March 19 of this year, this drug became the first AIDS drug to receive FDA approval. Zidovudine was also the first drug to be designated 1-AA, a category created in 1986 by Commissioner Young and me to assure that all potential AIDS and AIDS-related therapies receive FDA's highest priority — both in terms of quantity and quality of resources — under FDA's new drug review process. Approval of zidovudine was granted in record time — 107 days (about 3 ½ months) after receipt of the new drug application which consisted of a stack of paper some 20 feet high. The timeliness of zidovudine's review contrasts favorably to FDA's 36 month historical average review of new chemical entities and to FDA's current average of 24 months, and for this reason alone constitutes an important milestone in FDA's history.

More importantly, though, FDA's timely review and approval of zidovudine illustrates FDA's strong commitment to fighting AIDS. It was not the result of cutting corners. Rather, it was the result of better management and a high level of extra effort by everyone involved. Even though the review took only 107 days, the total FDA staff time devoted to the review of this drug came to approximately eight staff years, costing \$600,000 and requiring an intensive team approach.

INDS for other AIDS or AIDS-Related Drugs

By the end of the calendar year 1987, FDA had reviewed 164 investigational new drug applications (INDs) for some 85 different AIDS or AIDS-related drugs and biologics. Of these, 146 INDs have been approved and the drugs they cover are now being used in clinical studies related to AIDS. In many of these cases, FDA granted permission to begin clinical trials within a record 5 days of receiving an application.

Vaccines

On August 18, 1987, FDA granted permission for the first clinical

study in humans of an experimental vaccine for AIDS. This is an important first step in the development of a vaccine to prevent infection by the AIDS virus. The experimental vaccine, manufactured by MicroGeneSys, Inc. of West Haven, Connecticut, consists of purified protein from the genetic material of the human immunodeficiency virus (HIV) and was developed using recombinant DNA techniques similar to those employed in the manufacture of other recombinant vaccines. FDA approved a clinical trial for a second AIDS vaccine candidate in November. This vaccine, produced by Bristol-Myers Company of New York City, is made from vaccinia virus into which genes from the surface or envelope proteins from the AIDS virus have been inserted by recombinant DNA techniques. Clinical trials represent an important step in what is expected to be a long and difficult effort to develop a successful vaccine. Currently, FDA is reviewing several additional investigational applications from sponsors seeking permission to begin clinical testing of AIDS vaccines in humans.

Timely, High Quality Reviews

FDA will continue to assess the risks and benefits of potential AIDS therapies carefully and scientifically. If government is too rigid or too cautious in its decision-making, innovation can be hampered. On the other hand, if government is premature and hasty in its assessment of new products, public health can be put unnecessarily at risk. FDA is committed always to encouraging innovation, except at the expense of public health.

In its drug review process, FDA strives for consistency and scientific excellence. Decisions are based on data from adequate and well-controlled studies. Every feasible measure must be taken on a timely basis to evaluate safety and effectiveness. Judgment, by necessity, must play a major part in the review process: the same quantity of safety data cannot be required for a drug to treat a rare disease as for a drug to treat a common one; and drugs with dramatic effects on serious illnesses can be approved with less data than drugs that are not as effective. FDA's regulatory system must be flexible and timely enough to deal with urgent needs while remaining cautious enough to minimize risk.

The Blood Supply

In April 1987, FDA licensed the first Western Blot AIDS test kit

for commercial use in screening the nation's blood supply. The Western Blot method had previously been used only in a research setting for screening blood and for validating an initial screening of donated blood for antibodies to the HIV virus. The initial screening test, called the ELISA (enzyme-linked immunosorbent assay), was first licensed by FDA for commercial use in 1985. Although the ELISA test was designed for maximum sensitivity to eliminate all questionable blood and plasma, its increased sensitivity results in some false positive readings. Use of the Western Blot method, in conjunction with multiple ELISA tests, should help potential blood donors who have falsely tested positive by the ELISA method to be reentered into the blood donor pool, which is important, given the current shortages of blood and blood donors.

Condoms and Surgical Gloves

Surgeon General Koop has clearly enunciated the importance of the proper use of high quality latex condoms in reducing the spread of AIDS. FDA has accordingly increased both its public education programs and its inspection of manufacturers and processors of condoms. This includes programs for testing domestic and foreign-made condoms to ensure conformance with FDA's current good manufacturing practice (GMP) regulations. Any condoms not in compliance with FDA standards are recalled from the market. In a related area, FDA has begun a surveillance and sampling program to ensure the quality of latex surgical and examination gloves, which help protect health care providers from exposure to infection.

Fraudulent Products

When a firm makes fraudulent claims for AIDS products, FDA acts to remove these products from the market. FDA has sent regulatory letters to firms and initiated seizures of falsely labeled products. FDA has also taken action to stop the marketing of unapproved AIDS test kits promoted for home use. Efforts to combat AIDS fraud have been enormously successful.

To supplement these efforts, FDA has begun a series of Health Fraud Bulletins to alert our field offices so that they can move quickly against frauds when they arise. A National Health Fraud Conference cosponsored by FDA was held in March of 1988 in Kansas City, Missouri.

Research

FDA is also actively involved in conducting its own scientific research on a number of topics related to AIDS. This research includes studies of immunologic defects associated with the disease; the molecules that affect the immune system; and the biological and chemical properties of natural interferons and their ability to modify the immune system. FDA's basic, applied, and developmental research activities played a significant role in the development of vaccines, therapeutic agents, and test kits for possible use in AIDS and AIDS-related conditions. In addition, during this past year FDA has awarded contracts to outside academic researchers to conduct research on issues raised by the AIDS epidemic.

Public Education and Information

FDA is aggressively involved in making information on AIDS available to the public. FDA publications such as the "FDA Consumer", with a paid subscription list of about 18,000, and the "FDA Drug Bulletin" with some 1,000,000 medical professionals as subscribers, keep the public routinely informed on AIDS developments and other important topics. In addition, as part of its public education campaign, FDA has distributed instructions on the proper use of condoms and surgical gloves to reduce the risk of AIDS, developed an award-winning information package for the medical community, and publishes a monthly update on AIDS drugs and vaccines that are under development or review.

Conclusion

Compared to the pace of progress against life-threatening diseases in the past, progress against AIDS has been extraordinarily rapid. Because of the advanced state of scientific knowledge available only a few years after the disease was discovered, scientists have been able to precisely identify this deadly new disease and to discover its cause, the human immunodeficiency virus, in a relatively short time. Subsequently, FDA has approved diagnostic blood tests that make it possible to protect the blood supply, an effective therapy, and clinical testing of two vaccines. Yet the scientific complexity of the problem and the dimensions of its human toll remain staggering.

Combating AIDS remains FDA's number one priority. FDA's evaluation of therapies and diagnostics, and the agency's work in sup-

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port of vaccine development, will continue to make an invaluable contribution to the country's battle against AIDS. Until a cure and a vaccine are found, however, FDA as well as other PHS agencies will continue dealing with AIDS as a priority and encourage prevention through education.

PHS COORDINATION OF AIDS ISSUES

